With regard to the animal studies, the Sponsor did conduct numerous canine studies on various device generations. They did include a study of the final implant generation. With regard to the animal studies, there are no outstanding safety issues. Interesting to note, there was one case of tine penetration of the myocardium in one of the earlier device versions. However, there were no events seen on future studies using the final design.

In conclusion, there were no reported device embolization events, thromboembolic events, or device-associated early mortality events.

I'd like to briefly introduce the clinical trial design now. The PROTECT AF trial was designed to compare the WATCHMAN plus short-term warfarin therapy where short-term was defined as 45 days of therapy following post-implantation plus or minus a 15-day follow-up window. So WATCHMAN plus a maximum of 60 days of short-term warfarin therapy versus long-term warfarin therapy in the control group.

It was a randomized control trial with a 2:1 randomization scheme, unblinded, and the primary test was to test for noninferiority compared to the control, where the event rate in the WATCHMAN group was compared to two times the control rate or two

times the rate in the control group.

As the Sponsor mentioned in their presentation, there was a test for superiority. However, the device failed to meet the prespecified hypothesis test for superiority.

There were no additional tests for noninferiority or superiority for other analyses in addition to the intent to treat. Therefore, for example, individual endpoint components were not prespecified to be evaluated for noninferiority and superiority compared to the control.

The device was primarily studied in the United States, and there were four European sites as well.

As far as the primary endpoints, the primary effectiveness endpoint included freedom from stroke, and this included ischemic and hemorrhagic, cardiovascular death including cardiovascular and unexplained deaths, and systemic embolism.

The primary analysis was an intent-to-treat analysis, and a formal hypothesis test was established to evaluate the primary effectiveness endpoint.

The primary safety endpoint included freedom from occurrence of life-threatening events as

determined by the Clinical Events Committee. As mentioned by the Sponsor, there was no formal hypothesis for the primary safety endpoint as the primary effectiveness endpoint was considered to also encapsulate its safety events. Therefore, this endpoint focused primarily on periprocedural events and longer-term events related to bleeding or device embolization.

There were additional endpoints including primary technical and secondary endpoints.

With regard to the medical therapy specified in the protocol, WATCHMAN patients were to remain on warfarin if they were within 45 days post-implantation, and again, there's a 15-day follow-up window. So within 60 days post-implantation, they were to remain on warfarin. They were to remain on warfarin if there was incomplete occlusion of the left atrial appendage as established by transesophageal echo at the 45-day follow-up point. They were to remain on warfarin if the device was not implanted and also for any reason at the discretion of the treating physician.

WATCHMAN patients who were able to discontinue warfarin were per-protocol to remain on clopidogrel for 6 months post-implantation and for

aspirin for at least the duration of the trial. Control patients were to be on warfarin with a target INR of 2 to 3 for the duration of the trial.

Now, I'd like to introduce Dr. Sherry Yan, statistician, who will provide a statistical summary.

DR. YAN: Good morning. My name is Sherry Yan, and I will be presenting the FDA's statistical review of WATCHMAN Left Atrial Appendage Closure Technology submission.

First, I'm going to describe the study analysis plan, then I'm going to present the study primary endpoint analysis results, and some limitations of those analysis, specifically the prespecified statistical inference is based on a distribution assumption which is not supported by data and -- of confounding factors -- the interpretation of treatment effect. At the end, I will provide statistical conclusions.

My presentation will mainly cover the primary effectiveness endpoint, the only endpoint that defines study success criteria. A Bayesian model was proposed to evaluate the primary effectiveness endpoint. The number of events was assumed to follow a Poisson distribution with parameter lambda, where lambda is the event rate.

This model implies constant event rate over time. A noninformative prior distribution was assumed for lambda, and there were no historical data borrowed from other studies. The Bayesian approach can be considered approximately equivalent to a Frequentist approach because the prior is not informative and no historical data were borrowed.

A series of decision points were planned with the initial one at 600 patient-years of follow-up and subsequent ones at each additional 150 patient-years up to a maximum of 1500 patient-years of follow-up. At each point, the posterior probability distribution for lambda or event rate was to be evaluated to determine futility on noninferiority and, if applicable, superiority.

If neither futility nor noninferiority can be declared, an additional 150 patient-years of follow-up was to be collected before the next evaluation time point up to a limit of 1500 patient-years of follow-up.

If after the maximum of 1500 patient-years of follow-up, the new treatment cannot be established as noninferior to control, it would be considered not noninferior to control.

A flowchart of the study success futility

criteria will be provided in the next couple of slides.

Futility is declared in the posterior probability that the event rate for the device group is larger than or equal to the event rate for the control group is .95 or greater.

Non-inferiority is declared if the posterior probability that the event rate, lambda, for the device group is less than 2 times the event rate, lambda, for the control group is at least .975. In addition, to demonstrate noninferiority, the posterior probability that the event rate for the device group is less than the event rate for the control group must be at least .05.

Superiority is declared if the posterior probability that the event rate for the device group is less than the event rate for the control group is at least .95.

The primary analysis was specified to be based on the intent-to-treat analysis. The Sponsor also performed per-protocol analysis and post-procedure analysis, but neither one was ambiguously prespecified. Post-analysis -- in favor of device, for example, selection biased and calculation biased. Dr. Swain will discuss the limitation of this

analysis in detail.

Here I also want to correct one of the Sponsor's answer to the Panel question this morning. For in the Sponsor's per-protocol analysis, it include 36 patients who restarted warfarin.

In this statistical presentation, we will focus on ITT analysis only.

The Sponsor has conducted the primary analysis on the ITT population for both the 600 patient-year cohort initially submitted in the PMA and the 900 patient-year cohort submitted later. The primary endpoint observed rate shown in the table is the number of events divided by the number of hundred patient-years of follow-up.

The posterior probabilities in the table indicate that the primary effectiveness endpoint meet its prespecified noninferiority criterion with a noninferiority margin of 2 based on both the 600 patient-year and the 900 patient-year cohorts. But the prespecified superiority criterion is not met.

Please remember that in the primary effectiveness endpoint analysis, a constant event or hazard rate lambda for each treatment arm was assumed in order to assess this assumption. This picture presents the primary endpoint risk over six-month

intervals. The graph shows that the assumption of a constant hazard rate is not supported by data in the treatment arm.

As seen in the previous slide, the assumption of a constant hazard rate does not appear to hold. This is relevant in the assessment of the primary endpoint because the pattern and amount of follow-up will affect the study results. In this study, not every patient had the same follow-up period. The primary endpoint relies on a combination of hazard rate and amount of follow-up in each time interval.

The Sponsor also prespecified a Bayesian piecewise proportional hazards model with or without adjustment for CHADS score to calculate the 95 percent credible interval for the hazard ratio. It assumes that the Sponsor's conclusion regarding noninferiority is supported by this analysis. It should be noted, however, that the model assumes proportional hazard which implies a single hazard ratio, and the inference is conducted for this single hazard ratio, but the data do not support the assumption of proportional hazard.

In addition to the prespecified analysis, FDA calculated Kaplan-Meier curve of time to first

primary endpoint event and the probability of a having an event before time TEE for a number of TEEs. Kaplan-Meier estimates a clearly interpretable Kaplan-Meier methodology does not need assumption of constant hazard rate or ratio over time.

Here is a graph of the Kaplan-Meier curves and the confidence intervals. The red line is the Kaplan-Meier curve for the WATCHMAN arm, and the blue one is the Kaplan-Meier curve for the control arm. The shaded region represents the confidence interval. The red region is for the WATCHMAN arm, and the blue region for the control arm. Please note there is substantial overlap between the competence intervals. As expected, the control group has a wider confidence interval due to the small sample size as a result of 2:1 randomization.

This table contains estimates of probability of having an event before time TEE for TEE equals 6 months and 1, 1.5, 2 and 2.5 years based on 900 patient-year data.

Another major concern with the primary analysis is confounding. The study objective is to compare WATCHMAN plus short-term warfarin therapy against long-term warfarin therapy.

However, if we look at the 900 patient-year

dataset, in the device arm, only 293 patients discontinued warfarin at or before 60 days. Of the remaining 170 patients, 94 patients discontinued warfarin after 60 days or restarted warfarin later, and 76 patients were either without a device implanted or without warfarin discontinuation information.

In the control arm, only 157 patients stayed on warfarin. Of the remaining 87 patients, 84 patients had warfarin therapy discontinued or interrupted during the study, and three patients never started warfarin therapy.

This makes it difficult to interpret the comparison between treatment groups in terms of noninferiority. There are other potential confounding issues, and Dr. Swain will discuss it in detail from a clinical perspective.

In summary, the primary effectiveness endpoint appears to meet its prespecified noninferiority criterion, noninferiority margin corresponded to a doubling of event rate. However, the study results need to be interpreted with caution because model assumptions are not supported by data. Treatment effect is confounded with other factors.

Thank you. The next speaker is Dr. Swain.

DR. SWAIN: Good morning. So today my talk is probably going to be longer than normally you're used to hearing me talk because this is a very complex study. First of all, I'd like to say that it was absolutely wonderful working with the Sponsor. They're very responsive to all of our requests for data, an absolute pleasure.

Well, let's look at this trial design. So we're asked to look at a study regarding atrial fibrillation and thromboemboli. And we know from other studies that there is a question about the role of the left atrial appendage. In fact, there's the LAAOS study in progress now which is a study of 2500 patients with an endpoint at 5 years, looking at ligation of atrial appendage versus nonligation concomitant with coronary artery bypass in high-risk patients.

So the clinical question is really not answered whether all emboli in atrial fibrillation come from the left atrial appendage. Therefore, we have this study which is randomized which is very good because it gets rid of selection bias in the ITT analysis at least. Unblinded, it would be difficult, not impossible, but difficult to blind this study, so that we have the patients unblinded, the evaluating

and treating physicians unblinded and, of course, the CEC unblinded.

So we look at unintentional treatment bias. We look at assessment bias. We look at placebo effects. Those are some of the considerations we have to consider.

So, in its simplest form, we have a control of warfarin versus a treatment of the device plus short-term warfarin, and we've heard some about perhaps using this device without warfarin. It would be instructive for you to look at the animal studies. The first animal study used warfarin and the device. The second one did it without warfarin. It was found to be acute thrombus and then thrombin on the device. Therefore, the company in the third animal study used aspirin and Plavix. So the question of whether you can use this device without warfarin is really up in the air.

We have a 2:1 randomization that we've seen. We have a noninferiority hypothesis, and you're probably not used to seeing device versus medical therapy as noninferiority, but again when warfarin is the medical therapy, it would be wonderful to have a device where you had an upfront cost and then everything was fine and you didn't have

to give warfarin. As clinicians, we all know the difficulties of giving warfarin.

And then you wonder about this delta of 2 times control. Well, it's really a practical issue in that if the delta were much smaller than that, the sample size would have been phenomenal, so that one always at the end of the day looks at the clinical risk-benefit analysis rather than just the meeting or not meeting a statistical hypothesis.

What about patient accountability? And we can see that the ITT population here of 463 versus 244, and we have a couple of different things. Implant failures I'll talk about in a second. The no implant attempt. This is an interesting group in that one of these patients is the one that had the stroke after randomization prior to going to the cath lab to have an attempt. It's also instructive to look at the protocol in that patients have to be taken off warfarin in order to have this device implanted. So you look at that one patient who had the stroke prior to even having an attempt at an implant, his previous INR was 1.1, and he had a stroke. So part of the cost of this device may well be taking people off warfarin, and we know the vascular hematology group has a big controversy about

whether taking people off warfarin makes you prothrombotic or not, and that question has not been answered.

Another of those no implant attempts was a patient who had a complication of anesthesia for the procedure. Therefore, the procedure was aborted. So it's not an implant failure. It was classed as no implant attempt.

Also importantly, that only three patients never had warfarin. This is a study of patients who can take warfarin. There were virtually no patients in this study who could not take warfarin.

Okay. What about the reasons for the failure to implant, and this is a group that's not counted in that per-protocol analysis. Ten of them had myocardial perforations, one stroke from air embolism or an arrhythmia, and very interesting, two more patients that had a baseline TEE just like that previous stroke patient I talked about who showed no evidence of left atrial thrombus. Then on these two, they had the septum crossed during the procedure and were found to have thrombus in the left atrial appendage. Therefore, the device was not implanted. Again, the protocol required that the patient be off warfarin to have the procedure.

Okay. So who are the patients in this study? The requested labeling essentially for all patients with nonvalvular atrial fibrillation. So let's take a look at the enrollment.

Well, the demographics, there's really no baseline difference between groups, and this was a study in older white males as many of the cardiovascular studies are. And all the patients had atrial fib. They were relatively a low-risk group. There were 40 plus inclusion/exclusion criteria. Again, all of these patients had to be eligible for long-term warfarin because they could be randomized to the control group. The CHADS scale is 0 to 6, and this study included any patients with 1 to 6 on a CHADS score.

It excluded all patients with Class 4 heart failure, low EFs, anybody with a recent MI, recent stroke, or evidence of carotid disease. Also there was no dense spontaneous echo contrast, which is a relatively new inclusion criteria in the last 15 years or so in afib trials. When we look at the '80s, that's not a group that was excluded. This is a higher risk group again that was excluded.

When we look at the CHADS score, we can see that two-thirds of the patients were in 1 or 2, and

it's instructive to say that the AHA/ACC recommendations from 2006 feel there's enough evidence to think that there's clinical equipoise to treat this $CHADS_1$ group with simply aspirin rather than warfarin. So the choice is aspirin versus warfarin with clinical equipoise. So two-thirds of the patients were in the lowest risk CHADS score, and when we look at how the CHADS score is calculated, we could see that only a quarter of the patients had either heart failure or diabetes, less than half of them or so was greater than 75. Most of the one point addition is due to hypertension. Notice that only 18 percent had a previous stroke history, which gives you 2 points in the CHADS score. So there's a means CHADS score of 2.2.

Well, it's instructive to look at the types of analyses done. We look at ITT analyses, and again this is for the primary endpoint. This is the prespecified hypothesis. There were no events or patients excluded by definition from the ITT group, and as Dr. Yan said, in an ITT analysis, if a patient in a noninferiority hypothesis, if a patient doesn't get their assigned treatment, you essentially have a regression to the mean. So there is a bias towards the device. You're kind of pairing the same thing to

the same thing.

We look at the per-protocol analysis as defined by the Sponsor, and as Dr. Yan said, that patients who stop warfarin at the 45-day visit and then restarted were included in the per-protocol analysis.

So the control patients essentially excluded the three patients not treated with warfarin.

The device group excluded essentially anybody who had a bad result, less than 60 days or the 45-day visit. So anybody that didn't get the attempted implant, including that stroke patient that occurred before the attempt, anybody that had the implant attempted and had air embolism, myocardial perforation is excluded; anybody that did not discontinue warfarin or that we have information missing and finally anybody that had an event prior to warfarin discontinuation. So that was all excluded, and clinically that's probably not a very helpful analysis for us.

Likewise, the post-procedure analysis excluded events that happened on the day of the procedure.

So let's take a look at the differential

exclusions produced by these three prespecified analyses.

The ITT analysis, it's kind of a busy slide. What you see on the left is the percentage of patients included and excluded in each analysis. On the right upper is the number of efficacy endpoint events, and right lower is the number of strokes. So we can see in ITT by definition, nothing is excluded anywhere.

When we look at the per-protocol analysis, we can see in the control group nothing much is excluded. Very few patients in the per-protocol are excluded, but you can see that half of the endpoint events in the per-protocol are excluded, and 60 percent of the strokes are excluded.

Likewise, when we look at the post-procedure analysis, virtually nothing excluded in the control group, very few patients excluded in the treatment group, but we see about 25 percent of the endpoint events and 40 percent of the strokes excluded in that analyses. That's why we feel that these two analyses are really not helpful to us clinically.

What about antithrombotics? That's a big issue. We have several studies that look at

warfarin, aspirin on stroke studies. As Dr. Kelly, just mentioned, the ACTIVE trials, we have WARSS. I'm on DSMB for one of the largest stroke trials going now, which is the warfarin and aspirin and heart failure, and antithrombotics and warfarin, the use of both of them are somewhat confounding issues.

Well, in this trial, the inclusion criteria first again said that every patient was a candidate for warfarin therapy but didn't have to have warfarin therapy for another condition, and they could discontinue warfarin at the 45-day visit if there was no flow around the occluder.

The ringer here for a noninferiority trial is that by physician preference, they could continue on warfarin in this trial, and if the warfarin were discontinued at 45-day visit, then per-protocol, the patient was supposed to start on Plavix through the 6-month visit and continue aspirin throughout the remainder of the trial. So the confounder is the presence of antiplatelets and antithrombotics. And again, this is the same slide shown by Dr. Yan, but you can see that a third of the patients in each arm of the trial really didn't get the simple hypothesis divine treatment, which is control of warfarin, a therapeutic range, versus the device and short-term

warfarin. So this makes interpretation again of a noninferiority trial with a delta of two times somewhat challenging.

What are the reasons for restarting warfarin after stopping it at the 45-day visit? Well, nine of them really don't know, physician's order or unknown. Very interesting is the patient who at six months had a newly detected LAA flow where on the 45-day visit, there was no flow and the warfarin was stopped, and this may have implications for the need for follow-up and recanalization in these patients.

Also thrombus that was not present at 45 days on the echo in 2 patients were found at the 6-month and 12-month TEE, thrombus on the device. It's also important to note in this study, the core lab did not examine all of the echos. They examined apparently about 80 percent of the echos, but again can thrombus form after the warfarin is stopped, and it seems to indicate so at the 6-month and 12-month visit in these two patients. And does this imply a need for further monitoring of this device after the 45-day visit?

What about the percentage time on warfarin? There's several ways to calculate this, and the

Sponsor did it two different ways. They presented data on one way, and our statisticians feel that's statistically most appropriate, and I feel it's clinically most appropriate, to look at the percent of follow-up time on warfarin for individual patients and average those. That accounts for the uniqueness of each patient. It doesn't account for differential follow-up, but then it isn't weighted towards the longer-term follow-up in patients, in individual patients kind of correcting out the short-term follow-up. So I think this is the most appropriate way to do it, and if you look at this, we've got 87 percent of the control patients on warfarin and through the ITT analysis, 32 percent of the time for the device group for all patients and 23 percent for successfully implanted patients. So it makes it somewhat of a confounding issue again for a noninferiority trial with a delta of two times control.

Well, another way to look at warfarin use is how long you're therapeutic, and we have time in therapeutic range, the Rosenthal calculation, which was presented by the Sponsor, and that shows that, you know, it seems to be consistent with many trials. The problem with the Rosenthal calculation is it's

critically dependent on how well you monitored warfarin during the trial because it's a linear assumption between measurements.

If a patient only had two measurements in a year, like January 1st and December 30th, and both of those were in, then it would be 100 percent time in therapeutic range, when we know clinically that that's probably not a reasonable assumption. So one has to know, you know, how often these patients were monitored.

The protocol declared that the patients had two weeks monitoring in the first six months and then were supposed to have it monthly thereafter, and that fits the ACCP guidelines for Coumadin of once a month monitoring.

We can see here that about half the time they were in therapeutic range, but we actually don't know how often these patients had monitoring, and I'll bring this up in regard to some of the patients who had complications.

Well, what about follow-up time on medications? Essentially we have a trial here that's comparing the control group with warfarin, aspirin, Plavix, with the device plus warfarin, aspirin, and Plavix. So again we're looking at a noninferiority

trial and being asked to decide whether this device can replace warfarin, and that's the main question up to you as a Panel today.

Well, what about the results of the trial? Primary effectiveness endpoint were composed again of these five components, and it's important that, you know, we use a lot of composite endpoints because it's the only reasonable way to design some trial to have a reasonable sample size. But again, the components are non-hierarchically weighted. So we need to look at the individual components, and individual components are really not powered to detect differences. So we need to qualitatively assess that.

So, simply, here are the results from the primary endpoint, and it's important that primary endpoints may not fully describe the outcome of the trial, and as we note from this Panel, that meeting a primary endpoint doesn't necessarily mean approval of a device. Not meeting an endpoint doesn't necessarily mean disapproval of a device.

So let's look at the Sponsor's KM curve, and we can see that, you know, if there were just upfront loaded, you'd see the dip here and then go straight across, but we can see that there's a

continuing risk with this device, and you saw a KM curve on the per-protocol that showed, you know, a dip and then flat. Well, by definition, the per-protocol excluded any long-term events. So it's not surprising that you have a dip and then flat in that per-protocol, but looking at the ITT analysis, there seems to be continuing risk.

Then we look at the data that we have out to two years, and we see that there are really only 92 device patients, 52 control patients. So it doesn't give us a lot of data from which we have very wide confidence limits, and when we look at three years, we have very few amount of data. So we really don't know long-term durability of this device.

The Sponsor did meet the minimum requirements that we asked for follow-up.

Well, effectiveness is essentially the big ticket safety items in this study. It's kind of like a CPR study where, you know, stroke and survival are the endpoints. So we kind of have to look at this group of individual endpoint events.

Well, when you look at the primary effectiveness categories, we can see that the device had higher rate in ischemic stroke and systemic emboli, lower rates in hemorrhagic stroke and death.

So let's examine each of these.

When we look at deaths, it's important that the primary endpoint is only time to first event, and when we look at the long-term follow-up, there are actually three patients who had strokes in the device arm of the study who we have no data on since year 2006. So when we look at total deaths, we really don't know what happens. Differentially, there were more patients, three patients who dropped out of the study with no follow-up compared to one in the control group who had an event. So that is somewhat concerning.

When we look at time to first event, the endpoint deaths, we can see that the difference here, the relative risk is 3.3. When we look at all-cause deaths, we're down to a 1.6 relative risk. And we all have been on CECs. We know the problems.

It's just difficult to be on a CEC. We had the CEC charter but have never seen the decision rules, and a lot of times on CECs, we make decision rules ahead of a study and then things have to fit in them. So I don't question the CEC decisions at all. It's just that I don't have the decision rules, and I had somewhat of a difficult time deciding what their decision rules could have been. But again, there's

no question about it, but again we need to look at individual events in a qualitative way.

Let's just look at a couple of them. First of all, we had a control group patient who had stroke, had failure to thrive and pneumonia after a stroke, and this was linked to the primary endpoint of stroke. And compare this to two of the WATCHMAN patients, one of them who had a massive modified rank and a 5 stroke during device implantation, confined to a nursing home, died eight months later and was attributed to urosepsis, and this was not linked to the stroke. Certainly as surgeons, we all know that there are a lot worse things than dying, and having an MRA 5 or 4 stroke is one of them.

Look at the second patient here who had an ischemic stroke at implantation, right-arm weakness, transferred to a rehab unit with a modified rank and a 4 which is a severe disability, was transferred from the nursing home rehab to the hospital because of heart failure at two months later, and then two months after that, died of renal failure. Again, this was not linked to the stroke, and I'm sure that fit the decision rules of the CEC.

Finally, we have the device patient who had aortic and mitral valve endocarditis with a septic

embolus to the brain eight months after implantation, died of multiorgan failure. This was not an endpoint event. It's important to note that the implanters could choose any sort of prophylactic antibiotics that was according to their protocol at their hospital to put these in, and it was recommended that these patients be on the AHA prophylaxis afterwards for dental procedures and basic procedure.

Well, let's look at hemorrhagic events because one of the big reasons for this device would be this device versus the danger and the risk of warfarin.

Well, we can see here looking at hemorrhagic strokes that there were six hemorrhagic strokes in the control group, one in the warfarin group in a patient that had an INR of 5.8. It's also important, although not an endpoint event, that there was one WATCHMAN patient who had a subdural due to syncope two weeks after implantation of the device, but that's not counted in the primary endpoint.

So we look at these six patients with strokes. Three of them were on an appropriate amount of warfarin that was monitored within 30 days of the event. The other three did not have monitoring within 30 days of event. One was 39 days, one was 2

1/2 months, one was 3 1/2 months with no monitoring prior to their stroke.

So the Sponsor's talked a lot about learning curves on devices. I think we all know that the learning curve or the attention to detail in managing warfarin is a very important component of any patient taking warfarin.

What about ischemic events? The proposed labeling is using this device prevents the occurrence of ischemic stroke and systemic embolism.

Well, the control group have five ischemic strokes. One is a stroke that occurred two weeks after randomization during an AV junctional ablation procedure due to the procedure, a devastating stroke. And of the remaining four, none of them had evidence of therapeutic INR and appropriate monitoring prior to their stroke. One had a subtherapeutic INR at the time of the event, two did not have INR within 30 days of the event and had subtherapeutic INRs on the day of the event, one did not have INR data within 30 days. So all of the patients who had ischemic strokes, well, one of them due to another procedure, the other four, no appropriate warfarin use or monitoring.

Let's look at the WATCHMAN patients, all of

the ischemic events. We have 14 ischemic strokes, 3 percent, 2 systemic emboli, .4 percent, and then a TIA which was not counted as part of the primary endpoint, that was not a part of the primary endpoint. Well, we know about the one event pre-implant on a patient with an INR of 1.1 getting ready to have an implant. We have eight events that were temporally associated with the procedure. One was after a surgical explant of an infected device, two had an abandoned implant after a stroke during the procedure, and then there was this TIA which was somewhat confusing. It was called hemiparesis. It occurred the day after the procedure when the patient was sitting in a waiting room. The patient was "absent" for three to five minutes. The CEC adjudicated this as unresolved at five days, and it's not an endpoint event and, you know, the current definition by the TIA working group is things that don't resolve within 24 hours are generally called stroke, but this fit the predefined rules of the CEC.

And there were eight events past 30 days. One was on warfarin for flow around the device at 63 days. Seven of the eight were not on warfarin. One occurred 17 days after stopping warfarin. Again, is there a prothrombotic effect? The vascular

hematologists continue to fight about that one. And it's important to look at the time of these events, 2 months, 7 months, 8 months, 20 months, 22 months and 24 months.

Well, let's look at systemic embolism. It's kind of thought, well, this is sort of minor compared to death or stroke. Well, there were none of them in the control group, and there were two in the WATCHMAN group. One patient had a negative TEE pre-procedure, had been on warfarin. The protocol specified again, you have to stop the warfarin in order to do this procedure, had an INR of .9, and then after the transseptal puncture, a clot was found in the left atrium and the procedure was abandoned, and the patient had a retinal embolism three days later.

The other patient had a retinal embolism two years after implant. They were not on warfarin but were on aspirin and Plavix.

So the question comes about our ability in this trial to detect systemic emboli. There was no routine cerebral imaging. So subclinical strokes really could not be counted. There were no formal funduscopic exams. There was no comprehensive suite of neurocognitive testing, trail making tests, things

of that sort. So we only know a physical aspect of a stroke. That's the only thing that really could be picked up, and there's really no accounting for subclinical emboli to organs such as the kidneys.

Well, when we look at the presence of warfarin and during ischemic events, and here we have the ischemic strokes, systemic emboli, the TIA. It excludes the temporally related strokes and the pre-procedure event and includes roll-ins. We can see of the 11 patients with ischemic events, 10 were off warfarin during the event, 1 was on warfarin.

Well, the proposed labeling is that this is an alternative to warfarin therapy for patients with nonvalvular afib, and it's intended to prevent embolization of thrombi that may have formed in the LAA preventing the occurrence of ischemic strokes and systemic thromboembolism. So that's the main question to the Panel today, is that an appropriate approval, appropriate labeling.

Well, let's look at the primary safety endpoint. As you heard, there's really no hypothesis, no predefined composite. I had the CEC charter, but I didn't have the decision rules. So it made it somewhat difficult to understand attribution. And let's just kind of go over it. We have again the

simple safety endpoint two times the event rate in the control patients, but again the efficacy endpoint was really a safety endpoint, too. So this is somewhat of a subset.

What was in the primary safety endpoint, things like esophageal perfs from TEE, pericardial effusions, only those requiring drainage, things of that sort. Instructively, what was not counted in the safety endpoint, the patient who had a stroke after explant of the infected device was not counted as a safety endpoint. Ischemic strokes after day 30, all the control ischemic strokes were not counted. That's why there's that KM curve showing it flat after 30 days, 60 days.

Any WATCHMAN patients with myocardial perforations not requiring drainage, and as surgeons, we know that having a myocardial perforation, blood in the pericardium, may well comprise future cardiac operations. And thrombus in the WATCHMAN patients, if it didn't require hospital, I'll talk more about that later. So let's look at some of these events such as perforations, explants, emboli, thrombus and hemorrhages.

Myocardial perforations, it requires a transseptal procedure. Looking at all the patients,

there were 40 acute pericardial effusions that were myocardial perforations. The only ones counted as serious was if they need intervention, the 27. Of those 40, serious and nonserious, we look at first of all, there's an average of 14 cases per site, and you'd have to figure out in a practitioner whether they're going to get over the learning curve. First, one to three cases, 8 percent, greater than four cases in the randomized study, 7 percent.

Now, we've heard about the CAP data. The CAP data is 16 sites, 13 of which implanted more than one device out of the original 59 sites. So in the CAP data, there appears to be a decrease, but again that's a very limited number of sites, and I don't know what to make of that data. So looking at the randomized data, there appears to be, even after four cases, a substantial risk of myocardial perforation.

What about explants? The first one was a device that was seen to be perforating the left atrial appendage and was outside of the heart, had immediate operative removal. The other one was the patient I talked about with evidence of sepsis on day 4, and this was removed for presumed sepsis at day 16, and the patient had a stroke after that.

Look at device embolization, three of

those. It wasn't mentioned before on the description of that, but the one that was in the LV outflow tract required an open operation and required an aortic valve replacement due to injuries to the aortic valve leaflet. The other two were asymptomatic, and they were only found on protocol driven 45-day TEE, first percutaneous removal. The second one, the information we received is that the physician decided to just watch it, not that the patient didn't want it removed. So it was just a difference perhaps in the data that we received, and that was eventually removed several months later.

What about device thrombus? That's fairly interesting. There were 14 of these including the randomized and the roll-in patients. Thirteen of these fourteen were asymptomatic, and they were found on protocol-drive TEEs. As I've shown you before, there's really a limited ability to detect the clinical consequences of thrombus, thromboemboli, systemic thromboemboli. Two of the fourteen were not seen on the 45-day echo but were found on the 6- and 12-month echo, as I've said, which may have an implication for the need for continuing monitoring of these patients.

All 14 of these patients had the warfarin

restarted. Half of them had it stopped eventually in the study. Five of them had it continued throughout the rest of the study. Four, one of whom had a stroke, and that's why it was continued. So five of the 14 continued for the remainder of the study, and two of them had warfarin restarted because of an adverse event, and I really could not find the adverse event that caused that. So we can see that half of the patients eventually, you know, had this stopped.

Well, let's look at the two patients that were declared serious adverse events for device thrombus. The first one had the warfarin stopped at 45 days, but on the 6-month echo, extensive thrombus was found lining the superior lateral and probably anterior surface of the left atrium, including the WATCHMAN device. The patient was hospitalized. That's why it was called a SAE in order to start warfarin.

The other patient again had it stopped at 45 days for no flow and had an ischemic stroke three months later. The TEE at the time showed thrombus in the left atrium that was partially mobile in the far part of the left atrial occluder. Leakage was visible on the other side indicating incomplete

sealing of the LAA. So the patient had warfarin restarted. So this also has implications about whether these can recanalize.

Well, when we talk about warfarin, we always think, you know, the bleeding is the major problem. So looking at GI bleeding long-term is really interesting, and it's actually fascinating to note here that there's really a very small difference. It wasn't powered to detect a difference but a small difference in the rates of GI bleeding between the device group and the control group.

Well, what is this study not designed to determine? First of all, whether this device can be used in patients unable to take warfarin, and we can see reports in the press after the ACC meeting, a suggestion by one investigator, that they'd use these patients and people unable to take warfarin. This group was not studied in this investigation. All patients were eligible to take long-term warfarin. So we have no data on patients not eligible to take long-term warfarin.

Also, if you believe that there are other sources of emboli in atrial fibrillation besides the left atrial appendage, would use of warfarin, maybe even a lower dose and this device be additive

protection? Well, it's possible, and maybe a subset analysis or post hoc subset analysis would give you a hypothesis. We would view that as hypothesis generating and needed to be tested.

So these are the two groups of patients or the two situations that were not tested in this study.

What are our conclusions? Well, the WATCHMAN met the primary statistical effectiveness endpoint of noninferiority with a delta of two times the control rate. We need clinical interpretation, however. There's a liberal definition of noninferiority which was absolutely necessary for the trial design. There are confounding effects of both anticoagulant use in the device group not used in the control group, and antiplatelet medicines. The individual components of the composite and other safety events need to be examined.

In the safety evaluation, there appears to be a somewhat high upfront cost for implantation, meaning stroke, infection, myocardial perforation, and things such as thrombus and limited long-term follow-up, so that the chronic risk of thrombus accumulation, ischemic stroke, systemic embolus is not well quantified. So, thank you.

Our next speaker is Ms. Ellen Pinnow, talking about post-approval studies.

MS. PINNOW: Thank you, Dr. Swain. Here is an outline of my presentation today. First, I'll discuss the general principles that we utilize when thinking about the need for and designing post-approval studies. Then I will comment on the rationale for postmarket questions that the premarket study was not designed to answer but maybe address in a postmarket study.

Then I will summarize the latest version of the Sponsor's post-approval outline for the WATCHMAN device and provide an assessment of the post-approval study outline.

But before we talk about post-approval study, we need to clarify a few things. The discussion of a post-approval study prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable. The plan to conduct a post-approval study does not increase the threshold of evidence required to find the device approvable. The postmarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and

effectiveness in order for the device to be approvable.

There are two general principles for post-approval studies. The main objective of conducting a post-approval study is to evaluate the device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.

Post-approval studies should not be used to evaluate unresolved issues from premarket phase that are important to the initial establishment of device safety and effectiveness.

The reasons for conducting post-approval studies are to gather essential postmarket information, including longer-term performance of the device, including the effects of retreatment and product changes, data on how the device performs in the real world in a broader population that is treated by community-based physicians as opposed to highly selected patients treated by investigators in clinical trials, the evaluation of the effectiveness of training programs for uses of devices, the evaluation of device performance in subgroups of patients. In addition, post-approval studies are

needed to monitor for safety and effectiveness outcomes that may be of concern in the postmarket period.

Post-approval studies balance premarket burdens and can also address issues raised by Panel members based on their experience and expertise.

Post-approval studies should contain a fundamental study question or hypothesis, safety endpoints and methods of assessment, acute and chronic effectiveness endpoints, and methods of assessments. The post-approval study should specify a duration of follow-up.

There are three questions the FDA review team considered important in assessing the long-term safety and effectiveness of the device that may be addressed in a post-approval study.

The first question is what would be the real world performance of the device in a general population of patients and providers?

The second question is what is the long-term safety and effectiveness of the device in the postmarket period?

The third question, will the safety profile of the device vary depending on the experience of the operator?

The Sponsor proposed in the postmarket plan a post-approval physician education and training program and two post-approval studies. The first post-approval study is a long-term study, patients enrolled in the PROTECT AF pivotal study. And the second proposed study is the continued access approval study. I'll describe the proposed studies in more detail.

This table presents an overview of the Sponsor's latest post-approval study outline. The objective of the proposed post-approval study is to provide additional data on the long-term safety and effectiveness of the WATCHMAN device. The Sponsor proposed to follow patients enrolled in the PROTECT AF pivotal trial. The Sponsor proposes to follow the successfully implanted PROTECT AF trial patients for five years after the procedure. Patients will be contacted every six months by telephone.

The proposed evaluation of long-term safety is a descriptive analysis of life-threatening events at five years. This includes device embolization requiring retrievement and bleeding events related to the device or procedure. The proposed evaluation of long-term effectiveness is a descriptive analysis of stroke, cardiovascular death, and systemic embolism.

This table presents an overview of the Sponsor's latest post-approval study for the continued access post-approval study. The objective of this proposed post-approval study is to provide an acute evaluation of the WATCHMAN device and further characterize implant-related complications.

The Sponsor proposed a nonrandomized, open-label, multicenter trial. The study population consists of up to 200 subjects enrolled in the continued access registry and at least 100 subjects prospectively enrolled after market release at 10 non-PROTECT centers. The Sponsor proposes to follow these subjects for 45 days after the procedure.

The proposed evaluation of short-term safety is a descriptive analysis of serious adverse events following successful implantation of the WATCHMAN device. The Sponsor also proposes to describe the occurrence of life-threatening events, including device embolization, bleeding events, and other complications such as MI, TIA, death, stroke.

The long-term study proposed by the Sponsor is a descriptive analysis of long-term safety and effectiveness of successful implanted devices. All patients in the PROTECT AF study have been consented for five years of follow-up. The length of follow-up

is appropriate to evaluate long-term safety and effectiveness of a permanent device.

However, the Sponsor proposes only to follow patients who were successfully implanted with the WATCHMAN device. There was no long-term follow-up of unsuccessful and warfarin control patients proposed.

The safety endpoints are not clearly specified in the current proposal. The Sponsor should provide a detailed definition of the safety and effectiveness endpoints.

Finally, the Sponsor did not describe the current sample size and study design, and it is unclear if the study is sufficiently sized to evaluate the primary safety and effectiveness endpoints proposed.

In the afternoon, there are several questions we will ask the Panel to discuss.

What is the appropriate study population? Should this include unsuccessful implantation patients in a comparison group? And what are the appropriate long-term safety and effectiveness endpoints for the post-approval study?

The acute study proposed by the Sponsor is a descriptive analysis of the short-term safety and

effectiveness at 45 days follow-up. The proposed follow-up will not enable the assessment of long-term performance of the device in a real world population. Using the proposed design, the majority of patients will be enrolled at experienced sites, and this will not enable the evaluation of the safety and effectiveness of the device in a real world population.

The safety endpoints are not clearly specified in the current protocol, and the Sponsor should provide a detailed definition of these endpoints.

The Sponsor did not include a comparator group against which the endpoints could be evaluated.

The Sponsor did not describe the current sample size. Thus, it's unclear if the study is sufficiently sized to detect primary safety and effectiveness endpoints.

The Sponsor did not include a discussion on how operator experience could impact the safety profile of the device in a real world population.

In the afternoon, there are several issues we will ask the Sponsor to discuss. What is the appropriate study population? Should the population include unsuccessful implantation patients, and at

what clinical sites should these patients be enrolled? What are the appropriate safety and efficacy endpoints for this post-approval study? What length of follow-up is recommended? And is it important to evaluate how operator experience could impact the safety profile of the device?

Thank you.

DR. BUCKLEY: Thank you, Ellen. Thank you for your continued attention and endurance. This is the last portion of FDA's presentation.

I'm just going to review some of the questions that we're going to ask you to address in your discussion this afternoon.

The first question we have for you is with regard to device effectiveness. The key primary effectiveness results in the updated 900 patient-year dataset are shown in Tables 1 and 2 in the question handout in your Panel pack. The question is, do these data, in addition to the original 600 patient-year data, provide a reasonable assurance that the WATCHMAN device can be used as an effective alternative to warfarin treatment for reduction of stroke, death, and systemic embolism? Please discuss the confounding effect of adjunctive antithrombotic drugs that were given to patients in the device arm

of the trial.

Question 2 is with reference to device safety. Do the data provided from the PROTECT AF study provide a reasonable assurance of safety? In your discussion, please specifically comment on the incidence and significance of the pericardial effusions associated with use of the device. Please also comment on the incidence of device embolization and thrombus present on the device.

Third question is with regard to training. The pivotal trial demonstrated that qualified physicians need to carefully place this device in order to minimize acute procedural complications. Is the applicant's proposed training program adequate for training a new set of physicians in this procedure?

With regard to indications for use, please comment on whether the proposed indications for use statement appropriately identifies the patient population evaluated in this study.

Question 5, comment on the contraindications section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

And comment on warnings/precautions section as to whether it adequately describes how the device should be used to maximize the benefits and minimize adverse events.

Comments on operator's instructions as to whether it adequately describes how the device should be used to maximize the benefits and minimize adverse events.

Please comment on the remainder of the labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

Question 6, postmarket evaluation. Comment on the appropriateness of the proposed post-approval studies to assess the short-term and long-term safety and effectiveness, should include a discussion of proposed endpoints, length of follow-up, choice of study population.

Finally, by the way, we have to read this because it has to go in the transcript.

Please discuss if there's need for post-approval study to evaluate the implanting physician's experience and its effect on the performance of the device.

Thank you.

DR. MAISEL: Thank you very much to the FDA for an excellent presentation and we will open up for questions from the Panel. The questions are just for the FDA at this point. We'll have time to discuss further and ask the Sponsor more questions. So questions for the FDA. Dr. Somberg, you've had your hand up for about 10 minutes. You put it up before I even asked for questions.

DR. SOMBERG: Wow. Okay, whatever you say. I thought it was like 10 seconds. I was trying to help you along here.

I'm confused about many things here, but the one thing that I think is most salient is the question of comparing the device after its 45-day period, on Coumadin, when a patient no longer receives Coumadin to the control population, and I thought Dr. Holmes addressed that in slide 64.

However, Dr. Yan -- do I have your name correct? If I don't, I apologize -- said that was incorrect and that 36 patients still remained on Coumadin. Dr. Yan. Maybe, Dr. Yan, could you clarify that? Is that what you meant by that, that slide? You corrected -- you said you wanted to correct the Sponsor. So I take that to mean that you wanted to correct their statement to me about slide

64, or did I misunderstand that? And will you address or would Dr. Swain be willing to address the issue of what the FDA analysis shows of the per-protocol analysis of the patients who got the device and did not receive Coumadin after the 45 day plus/minus period?

DR. SWAIN: Dr. Yan has all the data, but the 36 patients that had warfarin stopped at the 45-day visit but some later time had it restarted were included in the per-protocol analysis. The Sponsor indicated they weren't. Dr. Yan's data indicates that they are included in the per-protocol analysis.

DR. SOMBERG: And you're specifically referring to their primary efficacy results in slide 64 of their presentation?

DR. SOMBERG: I think this is really critical to differentiate this population.

DR. SWAIN: Yes. The restarted ones were included in that by Dr. Yan's dataset that we received.

DR. MAISEL: We can have the Sponsor reclarify that issue later.

Other questions from the Panel? Dr. Resnic.

DR. RESNIC: I'm afraid that I might be

simpleminded about this. I think this is for Dr. Swain. A lot of your excellent discussion referred to the differences that the Clinical Events Committee attributed the first event or the association of event in the device versus the control. And so I'm still somewhat confused.

The issues of the air embolism and the subsequent strokes were not counted as ischemic strokes in the device arm. Is that correct?

DR. SWAIN: No, they were counted in the primary effectiveness endpoint. In the ITT, they were counted. Per-protocol, post-procedure, they weren't counted.

DR. SOMBERG: I thought that the air embolism wasn't actually accounted as a stroke. It was counted as a stroke?

DR. SWAIN: Yes. Yes.

DR. SOMBERG: It was counted as a stroke. And do we have an accounting for the ultimate survival analysis, that is, we have to first event, to first qualifying event. Do we have the analysis of overall survival? The Sponsor uses the terminology, it says only --

DR. SWAIN: Yeah, the endpoint. The endpoint is a time to first event. Therefore, if one

has a stroke and then you die from the stroke, the death doesn't count. You count just one event. It's just one per patient.

DR. SOMBERG: Yes.

DR. SWAIN: So that's why the secondary endpoint was all-cause deaths, which I've listed here.

DR. SOMBERG: Okay.

DR. SWAIN: Also, let me point out one error I made in my presentation. I talked about the Sponsor's KM curve that had the sharp drop and then flat. That wasn't the per-protocol. It was the safety analysis, and by definition, the safety was really procedure events. So that was an error I made in my presentation.

DR. MAISEL: Dr. Domanski.

DR. DOMANSKI: Yeah, I want to just make sure that I understand, you know, the analysis because I hear the various flaws, but I want to focus on just the intent-to-treat, primary effectiveness endpoint. Do you believe that the, you know, does your analysis suggest that what was included in that was true, correct, and complete? Now, I'm not talking about what they --

DR. SWAIN: Yes.

DR. DOMANSKI: Okay. And did you analyze the adjudication of hemorrhagic stroke?

DR. SWAIN: No.

DR. DOMANSKI: Okay. Thank you.

DR. MAISEL: Dr. Abrams.

DR. ABRAMS: It's a question for Dr. Swain, specifically about, it was on -- the slides aren't numbered, but it was about this TIA "hemiparesis" that you said was unresolved at three to five days. Did I understand that correctly?

DR. SWAIN: Yeah, it was unresolved at the time of discharge, which I believe was five days. So the only data I have is a narrative that talked about this hemiparesis of the left ankle, somewhere about leg not working, and then the CEC adjudicated it as not resolved at five days, TIA not resolved at five days.

DR. ABRAMS: So that was counted as a stroke, I take it?

DR. SWAIN: No, no. Absolutely not. It was counted as a TIA.

DR. ABRAMS: And there's no -- and you're not aware as to why the CEC might have not counted it?

DR. SWAIN: No, we can't -- we had no

decision rules for the CEC. So, you know, all I can say is this was not counted. We did not count it in the primary endpoint. I listed it under ischemic events because it's an ischemic event, but it's not a part of the primary endpoint.

DR. ABRAMS: Thank you.

DR. MAISEL: Can you or someone from FDA provide a little bit of the background regarding the noninferiority calculation and primary effectiveness endpoint, the idea that we would accept a device that was not twice as bad as the control?

MS. BOAM: Sure. I'm Ashley Boam. I'm the Branch Chief for Interventional Cardiology Devices at FDA. The endpoint, as Dr. Swain has explained, was largely driven by a desire to take a pragmatic approach to the trial design. We were trying to balance the need for an interpretable study with a reasonable sample size that could be accomplished by the Sponsor. We worked with the Sponsor very closely. We looked at a number of simulations that they conducted that indicated that there was actually a fairly low risk, that the ultimately relative risk in this study would actually be anywhere close to 2.

We also looked very carefully at the relative risk that was proposed, and to some of

Dr. Swain's earlier comments, if you try to look at a relative risk of say 1.4 between groups instead of 2, you very quickly get to a sample size in the 6,000 patient range, and if you tried to pull it down to something as small as 1.2, now you're talking in the 22,000 plus patient range.

We did have several caveats to this approach, however. We let the Sponsor know that we would certainly be considering the actual relative risk that was observed in the study and has been reported the upper bound on that relative risk, the 95 percent upper credible interval was 1.4, and that we would also be then considering the individual components of that composite in our clinical evaluation.

DR. MAISEL: Mike.

DR. DOMANSKI: You know, there's been a substantial question raised about the adjudication of hemorrhagic stroke. Did you do any of the mathematics to look at the sensitivity as, you know, in other words, suppose there was only one real hemorrhagic stroke. Then how do the results of this work out? I mean, do we understand that?

MS. BOAM: I can ask Dr. Yan, but I don't believe we've done that analysis.

DR. DOMANSKI: Okay. Because that could become a key issue if we turn around and decide that this was not appropriately adjudicated. All of a sudden the whole statistical, you know, the whole statistical basis for declaring it to be effective would deteriorate, at least probably evaporate is probably the right term.

DR. MAISEL: David.

DR. GOOD: Yeah, just a follow up that if I heard correctly, there was a fall with the subdural hematoma that wasn't called a stroke either. So that was on the control side. And I had one other question after that.

DR. SWAIN: Actually the subdural that I spoke about was in the device group two weeks after implantation, syncope, subdural and all that, and I believe there was also one in the control group, but they were not counted in the primary endpoint.

DR. GOOD: And one other quick question here. On slide number 11, there were a number of outstanding preclinical issues, some questions that the FDA had. I thought the Sponsor in one of their presentations had said that they had addressed those now.

DR. SWAIN: They did provide a written

response to FDA two days prior to this meeting. So far, that information has not been reviewed by FDA.

DR. GOOD: Okay.

DR. MAISEL: John.

DR. SOMBERG: There seems to be some differences in interpretation of the endpoints that a number of people have addressed between the Sponsor and the FDA. Was that discussed prior to this meeting, and has there been an attempt to resolve it? I don't see how a Panel can become an adjudication for each event in a timely fashion. So I would hope that the database we're asked to interpret is one that is mutually agreed upon or so egregious that each side is presenting, you know, an appeal.

MS. BOAM: Well, I can certainly assure you that we've had a number of interactions, both formal and informal, with the Sponsor asking for additional analyses, asking for explanations of datasets. God help me, I've even gotten into reading SAS codes. So there really has been quite a bit of back and forth with the Sponsor trying to make sure that we understand the dataset to the best of our ability.

As Dr. Swain has indicated, while we do closely review the narratives, it is not common for us to set aside, for example, a CEC adjudication of

an endpoint event. They're the experts sitting around the table at the time with all of the source documentation making that assessment. So the Sponsor's team may want to further address some of the concerns and the questions about some of those adjudications, but we have worked very closely with the Sponsor to make sure that we have as much data as possible.

As you noted, it's a very complicated trial, and depending on the way certain analyses have been conducted, you can look at some of the same issues and get somewhat different results.

DR. SWAIN: I guess I'll say that we have no disagreement on the primary endpoint numbers somewhere I have here. Hang on. So we have no disagreement on the primary endpoint numbers or what happened on the primary endpoint. So I don't think there's a controversy of that. We're not readjudicating events and pointing out events that occurred that are of interest, and I think at previous Panel meetings we pointed out things of interest. So there's really no disagreement.

DR. SOMBERG: So is it correct -- can I just follow up? Is it correct to state that in terms of the primary endpoint, that the FDA and the Sponsor

are presenting the data, so that what Dr. Domanski says is that if we change things, we will, you know, totally undo the presentations and the statistical analysis is not correct, that we are asked to give you our opinions on the dataset that is presented on the primary endpoint that is both agreed to by the Sponsor and the FDA?

DR. SWAIN: Correct. And, you know, as I pointed out in my talk, simply looking at the primary endpoint doesn't fully describe the trial. So we're describing some aspects. The Sponsor described others.

DR. MAISEL: Mike.

DR. DOMANSKI: Well, let me ask, maybe I could ask Bram and I want to make sure we've got this right. It's a two-part question. Number one is just, and, you know, I'm not trying to make a case that we should be setting anything aside. I just want to understand it because I think it's the key to this enterprise. One is, do you or do you not agree with the adjudication or do you simply not speak to the issue? And, number two is, is that a valid thing for us to look at, whether we think the data are, in fact, correct? So that's a two-part question. The second one for Bram.

DR. SWAIN: Well, we don't have the source data. We can't look at the adjudication. We don't even have the adjudication rules. So that's not a question we have.

DR. DOMANSKI: So you don't consider that. Okay. Good.

DR. LINDENFELD: But it is fair to say that you have brought up a couple of things that concerns you about adjudications. When is death not attributed to a stroke?

DR. SWAIN: Well, I'm not concerned about adjudication. I'm just concerned about events. So therefore just like myocardial perforations we've talked about previously and other things, bring up things that look to be of interest as a clinician.

DR. ZUCKERMAN: Okay. Let me address this. Again, as Dr. Swain pointed out, the data are the data, and this is the composite primary endpoint results. From our perspective, we're looking for the Advisory Panel to drill down on the significance of these results and weigh them against safety factors found in this trial.

I think it's fair to say that there are a few other associated things that Dr. Swain, Dr. Yan, and others from the FDA team have pointed out, but

that's to be expected in any trial. It would be more appropriate this afternoon for the Panel members to ask the Sponsor about their best recollection of events, but we're not suggesting in any way that these aren't the data.

DR. MAISEL: Do we have other questions from the Panel for the FDA at this point?

(No response.)

DR. MAISEL: So at this point, I'd like to open up the discussion both to Panel members who want to make observations or comments, if you have additional questions for FDA or Sponsor, we can do that as well. And I think I'll start by asking the Sponsor to respond to some of these questions regarding the adjudication of endpoints.

So we have been shown by FDA, and it's in our Panel packs, some questions regarding the adjudication of endpoints. Could someone please address that for us regarding the apparent discrepancy, for example, of a death in the control group that's attributed to a stroke with a similar death in the device group that's not attributed to a stroke as an example? Dr. Reddy.

DR. REDDY: Sure. We're going to go through this in detail after lunch. We have the

Chairman of the CEC, and we'll go over all of the rules for how these events were adjudicated. But specifically you're asking about -- there was some discussion about a TIA, I believe a little bit earlier. I just want to note that the event, the neurological event lasted three to five minutes. This is from the source documents. The ongoing, the reason why the CEC adjudicated this as ongoing after 45 days was because the patient was hospitalized and continued to be hospitalized after that point. It was not because of the TIA itself. So that's why it was adjudicated as a TIA and not a stroke, and therefore, it was not a primary efficacy event.

DR. MAISEL: Thank you. And it sounds like we'll hear a lot more after the break, which is great. Other comments from the Panel? Dr. Brinker.

DR. BRINKER: So I'd like to just ask in the all-cause death, there's 10 times by percentage rate incidence difference in cardiovascular deaths between the two groups. It seems bizarre. These are otherwise defined as probably coronary related, and I'm wondering whether this is just a statistical fluke, observational fluke, or whether the fact that the patients getting the device were on dual antiplatelet therapy for a good time or at least on

aspirin, whereas the Coumadin patients had half the incidence of long-term aspirin. So how do you make that --

DR. REDDY: Well, as you know, the study was certainly not designed to answer that question.

DR. BRINKER: Right.

DR. REDDY: But having said that, I think there are a couple of ways to look at this. I don't want to get into how the events were adjudicated. I mean that's something that again you'll hear in the afternoon about the actual rules. However, again I would point to all-cause mortality, probably the only endpoint in this study that nobody can really argue with, and I would again point out that certainly it was not higher in the device group. In fact, numerically it was 40 percent lower, 39 percent lower in the device group compared to the warfarin group.

With regards to potential other beneficial effects, coronary effects, et cetera, maybe it's true, maybe it's not true. However, I think we have to look at it as a strategy versus a strategy. In the Coumadin group, as you know, we do not want to put these patients typically on multiple antiplatelet agents for the obvious reasons of bleeding, et cetera. So these patients were treated as they would

in a real world fashion.

Beyond that, I think it's hard to really attribute the pathophysiologic mechanism potentially or just by chance higher cardiovascular deaths in one group.

DR. MAISEL: Did you want to respond to that?

DR. SWAIN: Yeah, I think, you know, the two issues are it's a statistical fluke or the device does something, or the other is that the device group had more contact with physicians. They had the 45-day, 6-month, 12-month TEEs. They won the coin flip, unblinded study, and got the new device. So one has to look at the effects of contacts with physicians, more adherence to medical care because we know the people that see physicians more often generally do better. So that's some of the factors that might be operative in this all-cause death issue.

DR. MAISEL: JoAnn.

DR. LINDENFELD: Let me ask I think Dr. Holmes, in slide 67 I think on page 34, it addressed the issue of the comparison of clopidogrel and aspirin versus warfarin and whether or not there was a benefit, and you presented the ACTIVE-W study saying clearly that clopidogrel and aspirin were

inferior to warfarin in that study.

But the question I have is that that ACTIVE-W trial was reanalyzed looking at the time in the therapeutic range, and what they found in the reanalysis of ACTIVE-W was that if you were less than 65 percent in the therapeutic range, there was no difference between warfarin and dual antiplatelet therapy. And in your study, the time in therapeutic range was 55 percent, suggesting that, in fact, there would have been no benefit of warfarin compared to aspirin and clopidogrel.

So, in fact, what I'm saying is that this is a really, I think, important point because it implies that it wasn't exactly a fair comparison.

DR. HUBER: I'd like to just clarify that because I presented that portion in terms of the two different analyses in terms of warfarin management. The first slide showed the number of INRs that were within therapeutic range. That was 55 percent, but then the following slide was the other methodology determining total time of treatment, and that was actually exactly the same as the ACTIVE-W study and was 65 percent. So --

DR. LINDENFELD: The time in the therapeutic range, the same analysis because time is

different.

DR. HUBER: Time in therapeutic range was 65 percent for the PROTECT AF trial.

UNIDENTIFIED SPEAKER: Dr. Huber, for the record, are you referring to your slide 33?

DR. HUBER: Yes, sir. So the PROTECT AF trial was at the top there, I believe, at 65 percent.

DR. LINDENFELD: Okay.

DR. MAISEL: Other questions from the Panel? I had a question regarding the acute procedural complications, and I just wanted to understand the roll-in part of the schema, if you will. I understand, A, that those patients in the roll-in had not been presented as part of the primary effectiveness. If you could explain when the roll-in part was instituted and how it worked, how it was decided how many patients at a given center were rolled in because looking on page 50 of 95, in the Sponsor Executive Summary on Table 10-2, it ranges from 0 to 5. Some places did 5 roll-in patients and randomized only 2. Others, you know, randomized 60 and had 3 roll-in patients. So I just want to understand that process is the first question.

DR. REDDY: Sure.

DR. MAISEL: The second question is going

to be I'd like to see what happened to those patients. I'd like to know how many of those roll-in patients had acute procedural complications.

DR. REDDY: Okay. So remember before -- we didn't talk about this, but before the randomized piece of the study, there was a pilot study that went on before, and all of those centers, or I think all of those centers, were actually in the randomized study. So those investigators did not do a roll-in. So the new sites were the ones that opted to have a roll-in phase, and they were allowed to have X number of patients, and it was up to the physician's discretion. Remember that the roll-in was a nonrandomized part of the study. So the roll-in, those patients would not be randomized, those three patients, et cetera.

And, because of that, most of the physicians opted for the roll-in. The exact numbers we'll get to you after lunch.

The second in terms of the actual data, we can also get you the roll-in data. We specifically left it out because we wanted to focus on the randomized cohort, but again we'll get it in the afternoon.

DR. MAISEL: So my concern is twofold.

Number one, the quote, "leaving it up to the site" alters potentially the population that we're seeing enrolled in the trial, and two is, when we're talking about learning curves and first, you know, three implants, it's really not their first three implants because they've already done some that we haven't seen the data on. So it's really their second three implants. So that has implications if we're going to start rolling this out to investigators about the training program and those sorts of things.

MS. LAAK: Linn Laak from Atritech. The roll-in phase was started in February of 2006. We did have a handful of centers that did not get to participate in the roll-in. When we discovered the need for a learning curve, we worked with the FDA to begin a roll-in phase. That roll-in phase was three patients per institution. The primary investigator was then to train the other investigators at that institution. Those first three patients then were in the previous group that didn't have the benefit of the roll-in, were still counted as randomized because those sites had randomized. We did have two institutions though that did have more than three because of an aborted case and therefore no ability to get any learning out of their learning curve three

enrolled. Those were protocol violations that we did note and push on, but everyone was allowed three per institution.

There were a handful of centers though that only did two and went right to randomization, but it was a per site roll-in and limited to the primary physician at the site. Does that answer your question?

DR. MAISEL: After lunch or after the break, I'd certainly like to see the data related to the acute complications to the roll-in phase.

DR. REDDY: Sure. The safety data, we actually did present. So the analysis for the first three patients, those were actually the roll-in patients or, in those few centers that did not have a roll-in phase, the first three randomized patients. So on the safety side, you actually do have the data. Did you want the efficacy data?

DR. MAISEL: No, I mean I was mainly interested in the safety issue.

DR. REDDY: Okay. So all that data is actually in the presentation, what you heard this morning.

DR. MAISEL: Yes, Jeff.

DR. BRINKER: Can someone tell me should

the device be approved, the labeling for the number of TEEs that a patient will have and the distribution of those. For instance, are they going to be late TEEs to look for some of the asymptomatic problems that existed in the study group?

DR. REDDY: That's a great question. I think definitely you have to have the 45-day TEE because that's the time you have to decide whether or not the device is fully endothelialized and there's no flowing you have to stop. Beyond that, I think it's something that we'll have to decide. What I can say is we can look at the data. There were a total of 12 thrombus events in this particular study out of 480 some patients who actually received the device. So that's a rate of approximately 3 percent. Of those 3 -- and which by the way, compares very similarly as you know to ASD closure devices which range anywhere from 0 percent up to 7 percent in terms of thrombus on the face of the device.

But of those 12 patients, only one actually had a clinical event that resulted from this. So that would be whatever, less than 1 percent.

DR. BRINKER: But some of the others had a pharmacologic intervention --

DR. REDDY: That's right.

DR. BRINKER: -- on that.

DR. REDDY: That's right. And of those 12 patients, 10 of those were recognized at the 45-day time point, but you're absolutely right. Two of them, so it is less than one percent, were recognized sometime beyond that 45-day time point. And that's something that we have to figure out, but again, two out of 480 patients.

DR. DOMANSKI: So let me ask just as long as you're up there, just to follow-up on two other potential labeling questions. How long are you going to suggest antibiotic prophylaxis, and how long are you going to suggest at least single antiplatelet therapy?

DR. REDDY: Well, in terms of antibiotic prophylaxis, most of the patients in this study just received antibiotics over the course of the hospitalization. So typically on the day of the procedure and that was it. There's no real data that we have that suggests anything otherwise would be appropriate. I mean certainly on pacemaker implants, et cetera, that's what we do.

I'm sorry. I don't remember your second question.

DR. DOMANSKI: The antiplatelet, how long

are you --

DR. REDDY: The antiplatelets. So this study, as you know, after the device is implanted, patients stay on aspirin forever. Patients stay on Plavix for six months. So after the 45-day time point up to six months, and at this point, we have no data that suggests, no clinical data to suggest anything otherwise would be appropriate, and that's what we would probably recommend.

DR. MAISEL: Tom.

DR. VASSILIADES: In the patients that receive the device that after 45 days underwent a TEE, did not have flow around the device, did not have thrombus, it's my understanding that the clinician at that point had the option to take the patient off of Coumadin and add Plavix. It wasn't necessarily required that they could do that. And so there must have been additional information that the clinician might be using to determine whether that patient could come off Coumadin, perhaps the CHADS score of that patient.

Do you have that information in terms of what the CHADS demographics or, you know, what the makeup was of those particular patients and perhaps what were the indications to remain on Coumadin? I'm

sure we're perhaps talking about a small number of patients, but these are sort of the biases that go into looking at the per-protocol analysis specifically instead of just focusing more on the intention-to-treat, but I'm curious as to what some of the factors were to staying on Coumadin.

MR. BULLOCK: At 45 days, if the physician taking care of the patient had reviewed the echo and the echo findings showed dramatic cessation of flow in the left atrial appendage, it was mandated that Coumadin be stopped unless there was a clinical indication that Coumadin be reinstituted or kept on at that point in time. And they were then switched to Plavix, and that Plavix was continued for a total of six months. And then at that point in time, the physician was able to stop that and continue with aspirin indefinitely.

This was a clinically driven point at that point in time. We did talk about mandating the use of the Coumadin and the Plavix for a certain period of time and the aspirin forever. But if other events occurred over the next course of a year that required that the patient resume Coumadin, and a small number of patients did that, then the physician did that. We did not mandate other cardiovascular care that the

patient --

DR. VASSILIADES: So if the patient had a CHADS score of 4 or 5, the clinician could opt to keep the patient on Coumadin.

MR. BULLOCK: They could.

DR. MAISEL: Dr. Kelly.

DR. KELLY: I have a question for Dr. Swain about your slide 61. In the device group, it looks like close to 60 percent of the patients were on Plavix. Is that total time during the trial that close to 60 percent were on Plavix, or some they got it part of the time and not all the time?

DR. SWAIN: They're putting up the slide here. My slide that has the calculation of the bars is based on taking each patient's total follow-up time, amount on X drug, that percent, summing up all the patients, dividing by N.

DR. KELLY: So nearly 60 percent of the time device patients were on Plavix.

DR. SWAIN: Correct.

DR. KELLY: Do we have any information comparing not on Plavix versus on Plavix outcomes or safety events?

DR. SWAIN: No.

DR. KELLY: And one other question, and

this may be more for the Sponsor, but I notice in the animal trials, they thought that Plavix, there was some evidence of Plavix inhibited some -- ingrowth, and I was wondering if stopping Plavix, if we'd see anything like we did when we did drug-eluting stents.

DR. MAISEL: Was that to the Sponsor or to Dr. Swain?

DR. KELLY: Either.

DR. MAISEL: Pick one.

DR. KELLY: The Sponsor.

DR. MAISEL: To the Sponsor. Can you comment on the duration of Plavix and --

DR. KELLY: And if we have any data --

DR. HUBER: If we could ask for a repeat of the question please.

DR. KELLY: Sure. It looks like about 60 percent of the time the device patients were on Plavix. And then there's some mention with the animal data that the Plavix seemed to somewhat inhibit the -- ingrowth, and I was wondering if we have any information that we might see something similar when we stop drug-eluting stent, when we stop Plavix in patients with drug-eluting stents, where there's less ingrowth and then we have a higher incidence of events.

DR. HUBER: Okay. Could you give me a second here?

DR. KELLY: Sure.

DR. MAISEL: While he's thinking, the FDA can answer.

DR. HAMPSHIRE: Hi, my name is Tory Hampshire. I'm the vet here at FDA.

I don't think we have an answer for what would happen if the Plavix and aspirin was withdrawn from the animal model. We did see that in the group of animals that were on study that received aspirin and Plavix, their thrombin, the thin thrombin coverage of the face aspect of the device was significantly reduced over that that existed without the aspirin and Plavix. Does that answer your question?

DR. KELLY: Thank you.

DR. MAISEL: Okay. The Sponsor can -- do you have a response to the question as well or not?

UNIDENTIFIED SPEAKER: No.

DR. HUBER: No, we don't, thanks.

DR. MAISEL: Okay. Thank you. Other questions or comments from the Panel. Dr. Fleming.

DR. FLEMING: I have sort of a stake in this issue personally. I personally suffer from

paroxysmal afib and I have a CHADS score of 1. So my question for the Sponsor would be was there any evidence of a worsening of the atrial fibrillation during the trial in the patients who received the device? For example, you know, once you implant a device like this, there's obviously would seem to me to be an opportunity for the afib to go from paroxysmal to persistent or permanent. So was there any evidence of a worsening of that condition?

I mean my distress as a sufferer is not necessarily due to my fear of a stroke. It's the disability that occurs when I'm in that arrhythmia, and I understand why we're all here today, but I do think -- I did not see any data having to do with whether patients were -- their condition was worsened.

DR. HUBER: We did not present any data, but it's my understanding that there was no difference in terms of whether patients were initially at paroxysmal atrial fibrillation that then evolved into persistent or permanent. There was no relationship with implantation of the device and the change in their classification of atrial fibrillation.

DR. MAISEL: Were there any patients that

had acute atrial fibrillation in the 24 hours post-placement?

DR. HUBER: No.

DR. MAISEL: Jeff.

DR. BRINKER: So following the $CHADS_1$ issue, if we agree that there's equipoise and that maybe you could have treated these patients in the Coumadin group with simple antiplatelet therapy or maybe not so simple antiplatelet therapy, the question is has anyone tried to dissect out whether at least -- take away the $CHADS_1$ cases and then determine whether there was a difference in the hemorrhagic stroke, hemorrhagic phenomena because that's where we all are really.

DR. REDDY: So we actually have data, and after lunch, we have some nice slides that addresses this question. The short answer is there is no difference. So if you look just at the $CHADS_1$ patients, if you take out just the $CHADS_1$ patients and look at the ones that are $CHADS_2$ or greater, there's no difference in terms of the efficacy endpoint. But we'll show you the actual data.

DR. MAISEL: David.

DR. GOOD: So this is kind of a proof of principle question from a noncardiologist. There are

a lot of other ways to ligate or eliminate the left atrial appendage. We've heard, for example, with bypass surgery, frequently the atrial appendage is ligated. And I realize that's a different procedure than what we're talking about here, but just in terms of proof of principle, what's the effectiveness of that in terms of decreasing a stroke? And I have to say I don't know the literature in that area.

DR. SWAIN: Well, that's why that LAAOS trial is in. There's a lot of, you know, single arm uncontrolled trials ligate that works, and as a surgeon I can criticize surgeons but, you know, we have no good level 1 evidence that this is the thing to do. That's why there's, you know, 2500 patients, 5-year endpoint studies in progress right now, and that's just a subset of the patients that may be at risk of atrial fib and emboli.

DR. MAISEL: Let's have the Sponsor respond to the same question please.

DR. HOLMES: Sure. The LAAOS Pilot Trial was published in American Heart Journal a couple of years ago. It looked at enrollment of 70 patients. Of those 70 patients, 20 of them were deemed not to be eligible for even an attempt. These were patients at relatively high risk for atrial fibrillation, and

then the Sponsor looked at an approach that either used staples or sutures.

The first piece of information they found is that 20 percent of the time, these were good surgical series, no question about that, 20 percent of the time, in 20 of the cases, they tore the left atrial appendage. Now, maybe that's not a big thing at the time of surgery, if you're watching it, except for the fact at least according to our surgeons, that's a difficult area to get to. So 20 percent of the time they tore the left atrial appendage under direct visualization.

Some of the time they couldn't use their device either because of lobes that were too close and they couldn't occlude it. The final piece of information that is of interest, that in the LAAOS Pilot Trial, which was a TEE trial, that was what they used in terms of evaluation -- that was the metrics for the response of the trial, about half of the time indeed, even though the surgeon said we have ligated it with sutures or with staples, they didn't because there was still residual flow at the time of follow-up transesophageal echo.

As I recall, a staple was better than suture but it was not universally the case. So the

pieces of information are that from a surgical standpoint, although highly trained surgeons can do it, some of the time the appendage is not suitable and some of the time they tear it and some of the time they say they ligate it but they don't.

DR. MAISEL: Dr. Swain looks like she has something to say.

DR. SWAIN: The LAAOS, you know, single arm pilot study, a very different patient population than this. Look at the inclusion criteria in this trial as to left atrial anatomy able to take this device. So it's a different group, and I think our surgeons on the Panel, you know, we all know that some days you don't see a left atrial appendage. It's just sort of this bump, and this particular trial we're dealing with today, it was not just a bump. It was a group that could have a discrete left atrial appendage which is very different to deal with than the bump.

DR. MAISEL: Thank you. Norm, do you still have a question?

DR. KATO: Well, I guess as a follow-up to that, is it clear that we know for a fact that all clot associated with embolic strokes from atrial fibrillation originates from the left atrial

appendage because otherwise we're going to be putting a bunch of these things in left atrial appendages and the clot could be forming someplace else.

DR. SWAIN: Well, that's exactly the question we're asking you to look at when you evaluate this trial and the concept of the trial. Is it a replacement for warfarin? Does it abolish ischemic events? That's exactly the question you all need to deal with.

DR. KATO: But --

DR. SWAIN: I'm not answering it for you.

DR. KATO: You've asked me to deal with the question about treatment. I've asked you the question about etiology and mechanisms --

DR. SWAIN: That's right.

DR. KATO: -- of -- I mean do we have scientific evidence, you know, pretty good evidence saying that 100 percent of the time or 90 percent of the time we know that that clot comes from the left atrium and that by fixing that, the clot won't come from anywhere else?

DR. SWAIN: No. Level 1, there are no level 1 evidence to indicate that. That's why it is being studied and is proposed to be studied by various surgical groups also.

DR. KATO: So this is still up in the air.

DR. MAISEL: So in our Panel packets presented to us is 90 percent of clots come from the left atrial appendage in patients with atrial fibrillation, and I certainly understand the level and the quality of data. Do you dispute that number?

DR. SWAIN: I don't find level 1 evidence to support that number, and I don't find any studies, you know, the only study that can do that is a study like this that says you get rid of it, do you then get rid of 90 percent of the strokes or virtually all of the strokes or ischemic events? And it's only due to the left atrial appendage. That's the question you're really asked to answer here.

DR. MAISEL: Why doesn't the Sponsor response to that issue as well, please.

DR. REDDY: I just want to speak to that. Again, as Dr. Huber presented earlier, the data that we have which is not level 1 evidence, as Dr. Swain just pointed out, but the data that we have is based on autopsy data and TEE data that shows patients with nonvalvular atrial fibrillation, when a clot is seen, 90 percent of the time it's seen in the left atrial appendage.

DR. KATO: Can you slow down a little bit?

Your words are slurring over, and I can't understand what you're saying. I'm sorry.

DR. REDDY: Okay. That the date that we have is that in patients, and this is from autopsy series and TEE series, so in patients who have had a stroke who underwent a TEE or again an autopsy, when a clot is seen in the left atrium, it's in the left atrial appendage. It's 90 percent of the time.

Now, what do we do in this study? In this study, we try to enrich to some extent the patients who would be most likely to have the left atrial appendage as the pathogenesis of a subsequent stroke. So, for example, we excluded those patients who had significant carotid disease, who had left ventricular dysfunction but potential ventricular aneurysms and clots, et cetera.

So in some sense we enrich for those patients, but ultimately you have to look at, this is the first study, as Dr. Swain said, that has randomly assessed both the question of the pathogenic role of the left atrial appendage in stroke as well as in this particular case, a particular device trying to address that.

And if you look at again the fundamental data, if you look at the intent-to-treat analysis and

primary efficacy endpoint, we have noninferiority and numerically 39 percent decrease of event rate. No, I said that wrong, I'm sorry, 32 percent decrease of event rate.

DR. MAISEL: Okay. Thank you. At this point, I think we'll take a break. We'll have lunch, and we will reconvene in 45 minutes at 20 past 1:00.

(Whereupon, at 12:35 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:20 p.m.)

DR. MAISEL: Good afternoon. We're going to get started.

The Panel had asked a number of questions of the Sponsor who is now prepared to answer them. So they're going to take about 10 minutes to answer some of our questions and present some data.

DR. LEW: Brian Lew again. I was head of the CEC Committee for this study, and there were a lot of questions that came up about the adjudication.

The members of the Committee included myself, an interventional cardiologist, as well as a second interventional cardiologist and a neurologist. In addition to the voting members, we had outside consultants. A neuroradiologist who reviewed all of the scans independently of the stroke events, as well as a neurologist who independently also reviewed the charts and records that were available, and he was a stroke specialist from Minneapolis Heart Institute.

The documents we obtained included all the source documents that were presented to us as well as any documents that we would request from the site. A lot of the summaries that the FDA got and are listed in these tables are summaries from clinical

nonphysician personnel, and we went from the source documents when we requested it. We tried to get all of the records, the scans, the neurology reports, the discharge summaries and so forth.

We spent a lot time with the definition of stroke and especially hemorrhagic stroke because of the ambiguities of some patients when they present. A lot of times you have somebody who suddenly falls or is found on the ground, they have a subdural and parenchymal bleed, and the question is which came first, the chicken or the egg, and we had a hard time deciding how to deal with that.

We did have predefined definitions before the study, and we decided to, in order to allow us to do this in an unbiased way, to classify all bleeds, intracranial bleeds as hemorrhagic strokes. You can argue with that definition, but it made our decisions much easier to make and adjudicate.

Subdural hematomas that were traumatic without any extension into the intracranial area was considered a subdural bleed only.

If we look at the three cases where we talk about traumatic hemorrhagic stroke, one patient was found on the ground. It was an unwitnessed fall. He was found to have a very large subarachnoid hematoma

and eventually required a feeding tube. Again, we're unclear what came first.

A second patient presumably fell and was found at the bottom of a stair. He had a subdural hematoma on CT scan as well as intracerebral bleeding, and he eventually had problems with walking and communicating.

The third patient fell on the ground. He had a subarachnoid hemorrhage and occipital contusions. The neurosurgeon reports that he was unable to tell if it was a bleed from aneurysm or from trauma. The outcome unfortunately in that patient was death.

The next patient is a gentleman who developed sudden symptoms of headache, vomiting, and the typical finding of a intracranial hemorrhage, and eventually died.

The next patient had sudden onset of dizziness, confusion, nausea and vomiting, and was found to have a cerebellar bleed on the right side on scan.

And the next patient presented with confusion, mental status changes, and had a subdural hematoma with no intraparenchymal hemorrhage.

Based upon the definitions we defined on

the previous slide, we decided that these were hemorrhagic strokes. I hope this clarifies our definitions.

The other thing that came up was not only did we have these predefined, we had a whole list of things that were predefined as far as what constituted a stroke, what constituted a pericardial effusion, and so forth.

DR. HOLMES: If I could just on this specific point, but it seemed to be of considerable controversy. As we think about the hemorrhagic strokes in study patients, it's very, very difficult and can be confusing. If we come across a person who is down and then are found to have intracerebral bleeding, it is hard to be sure whether they have fallen or not.

We do know that the PROTECT AF trial was a randomized trial. That is true.

The second piece of information as we have just heard that the CEC reviewed all the bleeding events in both groups. This wasn't just the warfarin group. It was both groups, and they did adjudicate them according to the prospective definitions. These were definitions that were set up ahead of time. So we were incredibly keen that they had allowed us

to -- those definitions ahead of time so we could accordingly diagnose and put the patients where they belonged.

The third is that we could expect trauma to occur at similar rates in both groups. There isn't any reason to believe that those patients on Coumadin would be more likely to have trauma. They might be more likely to have problems with that trauma, but they weren't more likely to have a problem because those patients that do have trauma that are on warfarin would be more likely to have a head bleed.

For those of us that work in emergency departments or receive patients, if a patient comes in having been in an accident and they are on warfarin, they have the band on that says I'm on warfarin, we immediately suspect that there is going to be head trauma, and we oftentimes get more CT angios, get CT scans just because we treat them differently because of the potential for bleeding from a clinical standpoint. Next slide.

This is the data on hemorrhage of patients on warfarin. Those patients, as we've mentioned, with minor head trauma who are anticoagulated are increased risk of intracranial hemorrhage. These are the citations in the lower right. The warfarin

increases the risk of spontaneous intracranial hemorrhage up to 10-fold, and in those patients with head trauma, mortality rates range from 50 to 77 percent.

Now, as we think about the trial, we saw the hemorrhagic stroke data. Four of six hemorrhage strokes that have been adjudicated by the CEC died, 66 percent, right in range with what we see on this trial side, where in-patients with head trauma, mortality rates range from 50 to 77 percent in those anticoagulated patients with intracranial hemorrhage.

And finally patients with anticoagulated hemorrhage have a fivefold increased risk of death, Fivefold increased of mortality.

And so as we think about it, I think that the most important point is that these patients died with what we called intracranial hemorrhage. This was the group of patients on warfarin therapy. Had we adjudicated them differently, just as death, they would have fallen to the death column, and they would have counted in the death column. And so irrespective of that, they could either have fallen in the stroke column, which was worse, or in the death column, which would subsequently become much more worse.

And so the bottom line is it is difficult sometimes to adjudicate that completely, but it's a very high risk group of patients when they fall, when they have head trauma with warfarin. They bleed into their heads with subsequent major increase in mortality.

DR. MAISEL: You can have another minute if you have something to respond to, or we can ask additional questions as they come up. Your preference.

DR. HUBER: Actually, we just had a couple of other issues that we thought were going to come up. I was going to talk a little bit more about the patient where there was a question of possible infection that would have required explant, and if the Panel wants to hear more about that, I'd be happy to share that.

DR. MAISEL: Okay. Why don't you hold off on that for now. Let's try to have some discussion regarding the issue that was just discussed or if you have other --

DR. REDDY: I just wanted -- there was a question before about TEE data.

DR. MAISEL: Yeah, let the Panel try to resolve some of these issues, and then we can come

back to that, and Dr. Abrams, do you have a question or a comment?

DR. ABRAMS: Yeah, I just want -- just for my own clarification, so I understand. I'm making a distinction -- there's intracranial hemorrhage, and there's intraparenchymal intracerebral hemorrhage.

Most neurologists would say that intracranial hemorrhage does not necessarily have to come along with injury to the brain. So you can have a subdural hematoma from trauma that has nothing to do with stroke. A lot of times the intraparenchymal and intracranial seem to be, I don't know, in some cases I've seen intraparenchymal and sometimes I see intracranial.

If you go back -- could we go back to Dr. Lu's -- your own definition or the definition I'm seeing that there's supposed to be tissue damage that occurred. Now, and one of those individuals who fell had a subdural hematoma. You're saying that you're adjudicating that as stroke as based on this tissue damage, but all I'm really hearing there is that he had bleeding in the subdural space. And that's just -- which is obviously an adverse event and any kind of bleeding like that is very serious and could lead to death, but it's not technically in my mind a

stroke.

DR. LEW: The definition of stroke we struggled with a lot, and both as a nonneurologist as well as with our neurologist on the Committee and our consultants. We decided any bleed with a sudden neurological deficit was a stroke, a clinical event, and whether it happened in the brain tissue, the parenchymal or subdural space, when there was a neurological event, the patient suffered some injury, that that was a stroke.

DR. ABRAMS: Okay. And so you did not require necessarily that there be brain damage per se. It would just have to be a sudden change in neurological status.

DR. LEW: And it had to meet the criteria for a stroke, something that lasted 24 hours, yeah.

DR. MAISEL: Mike, you had a lot of questions earlier about this issue. Do you want to comment?

DR. DOMANSKI: Yeah, I mean I think that's a reasonable explanation frankly.

DR. LEW: Yeah, I understand. You could look at that table and say, you know, we adjudicated it wrong. We did our best. There were cases where the site reported a postoperative patient was

mentally deficient, excuse me, was confused, and we looked at it and we decided it was a stroke.

DR. MAISEL: Are there other Panel comments regarding just the issue of adjudication of events that we've just heard about, other comments or observations? Fred.

DR. RESNIC: Just a quick question. The CEC, you were not blinded to the assignment. Is that correct? You knew which, or were you blinded to the assignment, whether the patients, in fact, got the device or did not get the device. It's --

DR. LEW: It's pretty hard to be blinded to a device study.

DR. RESNIC: Unless the records were scrubbed, but they were not in your case.

DR. LEW: Well, you know, if somebody has a pericardial effusion, somebody has an embolization, we know very much whether it's a device or not.

DR. RESNIC: So the answer is no.

DR. LEW: That's correct.

DR. RESNIC: There was no attempt to keep it sequestered, that is --

DR. LEW: No.

DR. RESNIC: Okay.

DR. LINDENFELD: Were there substantial

differences between how the investigators classified these endpoints and how the CEC did?

DR. LEW: I don't think anybody's done that analysis. I mean there were cases where we overrode or whatever, we changed the diagnosis from the site-given diagnosis on the case report form to what the CEC decided. Yes, there were changes. I gave one example where they said it was medication effect, and we decided it was a stroke. There are cases where we upped the code to a stroke and we lowered a code to a stroke, but we based it on the source documents that we have available to us and all the documents that we could get a hold of.

DR. MAISEL: So thank you very much. I think that really helped clarify that issue.

Dr. Reddy, did you want to talk about the TEE pericardial effusion issue briefly?

DR. REDDY: Sure. This is a fairly -- slide but can we -- yeah, okay. So this shows the TEE results. What you see in the top column is a follow-up, and it was a TEE, 45 days, 6 months, 12 months, and 24 months, and what you see, the reasons for continuing warfarin at these various times, you can see initially the majority of the reason was because of LAA flow. You see that in 30 patients,

and 13, 9, and 0. And you see various other reasons. Physician order, thrombus, adverse event, embolization, explant, or planned procedure where there's ablation or otherwise.

I should note that some of the physician order indication also included some of those planned procedures as well as some other various events.

DR. LINDENFELD: And, Dr. Reddy, can you tell us what percentage of patients had a TEE at each of these time points? I mean is this 90 percent of all the patients or 70 percent, or does it drop off?

DR. REDDY: Yeah, it certainly does drop off. This is, again, all the patients. It's a continuing follow-up.

DR. LINDENFELD: I know the number of patients drops off, but should the percentage that had a TEE first that were followed change?

DR. REDDY: Yeah, I can give you approximately. There are approximately 200 some patients at the 6-month time point, but beyond that, we can look back at the Kaplan-Meier curve. Let me see if I can find one of those to see if we have that. Can we show any of Kaplan-Meier curves? He's going to pull up one of them, but you'll see at the very bottom, how many patients are each of the time

points, and you'll get some idea.

DR. LINDENFELD: Is that number after the number of days, is that the number of TEEs? In other words, after --

DR. REDDY: Well, the Kaplan-Meier data is written as number of days.

DR. LINDENFELD: No, but the previous --

DR. REDDY: The previous slide was TEE. TEE is 45 days, 3 months, 6 months, and 12 months.

DR. LINDENFELD: No, but you had a number in parentheses after the 45, 52. Is that the number of patients that had a TEE at that time?

DR. REDDY: No, no, it wasn't. Can we go back?

DR. LINDENFELD: What I'm just wondering is how many of the total number of patients that were going to have a TEE actually had them.

DR. REDDY: Oh, I see. The majority of the patients who reached the time points, over 90 percent of the patients who reach any specific time point and were supposed to have a TEE had a TEE. So it's actually much higher than that. I just don't have the exact number.

DR. LINDENFELD: Okay.

DR. REDDY: So virtually all the patients

who were supposed to have a TEE at their specified time point did actually have that TEE done. Is that the question?

DR. LINDENFELD: Right. It's over 90 percent?

DR. REDDY: Over 95 percent. Well, it's 97 or 99. I just don't know.

DR. MAISEL: Okay. Thank you, Dr. Reddy. So at this point, we can open it back up, if the Panel has any other questions for FDA or the Sponsor or wants to make comments or observations, and then once we spend a few more minutes doing that, we'll move onto the questions. Dr. Somberg.

DR. SOMBERG: Yes, I'd like my question addressed, the discrepancy between what the FDA and the Sponsor had, to Dr. Holmes specifically. Can you address, what was it, your slide 64? When I asked you previously if that material or the database that it's based upon compared the patients who after 45 days stopped Coumadin with those people in the control group that were on it, the statistical lady from the Agency felt that there were a number of patients who were still continued, who were placed back on Coumadin in that group. I would like someone to show me the data where we contrast the device

without Coumadin over the rest of the study with the control group on Coumadin. That to me is a critical question.

MR. MULLIN: I am Chris Mullin, a consultant to Atritech from the Integra Group. I have no financial stake in the company, but I'm compensated for my time and travel today.

Your question with regards to warfarin use, there was a little bit, I think, misunderstanding earlier about the definition of the per-protocol analysis as included in the clinical report. The per-protocol analysis that was included there did count everything that happened from the time of warfarin discontinuation onward. So if a patient restarted, that patient would be included.

However, we did perform an analysis where we'd take those patients who restarted out of the per-protocol analysis, and indeed those results improved further in favor of the device, and the relative risk approaches zero, more in favor of the device.

DR. SOMBERG: Do you have that slide or data?

MR. MULLIN: We have a number of analyses presented on this slide and the next one. The FDA

did ask for several different variations on the per-protocol analysis to clarify, I think, the very issue that you raised with regard to continual confounding.

No matter what analysis we did, I think the on-treatment analysis in the bottom row is the closest one where if a patient restarted warfarin, their data was censored at that time point in the device group.

I think in all of these analyses including the ones on the next slide, and you see relative risks further in favor of the device, approximately in the range of .5 to .6.

DR. SOMBERG: Okay. With that said, now if people who had to go back on warfarin, one could say, well, they had some clinical problem and that might be a toxicity and that's why they had to be put on it. So while the efficacy might go up, you know, the toxicity might go up or the adversity. Can you balance that for me? Because what I'm trying to say is I would like to have a risk-benefit analysis based on device versus Coumadin because that's what this device is indicated for, and I can't believe that we can't get that succinctly stated.

DR. HOLMES: I think simply stated, it didn't matter whether we analyzed the patients that